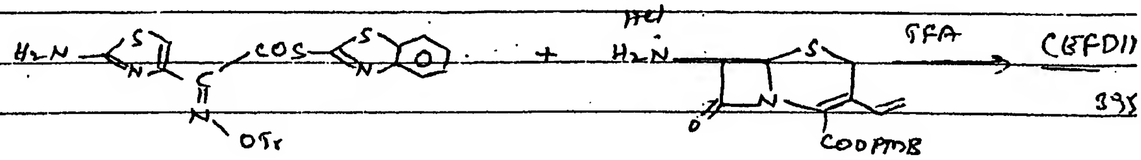
EXHIBIT A

[redacted] Condensation And Deprotection PR(094) 94

Objective: Preparation of condense amide.

Reaction Seq:—



MW: 578 MW: ~~405.0~~ 382.5

S.No	Raw materials	mol wt	moles	Amount	Mol. ratio	Source.
1	7-AE · HCl salt	~~405~~ 382.5	0.0493	20 gm	1.0	
2	DMAC	—	—	100 ml	5T	comm
3	Thio ester	578	0.0493	28.5 gm	1.0	PR/88
4	TFA	114	—	105 ml.	3T	comm.

Procedure:— DMAC was added at RT.

Thio ester was added in one lot at the same temp.

The mix was stirred for 5 min.

Almost clear solution was formed.

HCl salt was added in one lot.

Stirred the mix for 2.0 Hrs at 40-50°c. (pH was maintain ~ 3-4) c̄ TEA

TLC was showing ~ 2-3 % of thioester.

Reaction mix (clear soln) was cooled to 10°c.

DCM was added (250 ml) at the same temp.

DM H2O (250 ml) was added in one lot at 10-15°c.

Stirred for 5 min.

layers separated.

Aqueous layer was again extracted with 250ml of DCM.

Combined Organic layer washed with DM H2O (100 ml X 3) + 30ml brine soln each

Organic layer (treated) washed with 1% NaOH soln for 1.0 Hr.

layers separated.

Organic layer wash c̄ brine soln (100 ml).

Dcm was distilled off at below 40°C u/vacuum.

To get the 'dark coloured residue.

To this toluene (400 ml) was added and codistilled ~100 ml u/vacuum.

Toluene layer was cooled to 10°C.

TFA was added over a period of 30 min at 10-15°C.

After addn, stirred the mix at 15°C for 3.0 hrs.

Dark coloured rean mix was cooled to 0°C.

Dm H_2O (350 ml) was added and stirred for ~~the~~ 5 min.

layers separated.

Note:— During the layer separation, solid was formed.

then the pH was adjusted to 4.5 by adding Aq NH_3 soln,

Then layers separated.

Aqous layer was cooled to 10°C.

Carbon (2 gms) was added and stirred for 30 min.

filtered through ~~Carbon~~ hyflow, washed c̄ DM H_2O (50 ml).

filtrate (AL) was cooled to 10-12°C.

pH was adjusted to 1.1 by using conc HCl soln.

White solid was obtained.

Stirred the mix for 30 min at 0-5°C.

Solid was filtered, wash c̄ ML (50 ml).

Solid was treated with 350 ml of Dm H_2O at 30-32°C for 30 min.

Then cooled to 0-5°C for 30 min.

filtered the solid, washed with Dm H_2O (50 ml), (5°C).

Dried the solid at 35-40° u/high vacuum for 5 hrs

Dry wt = 9.0 gm

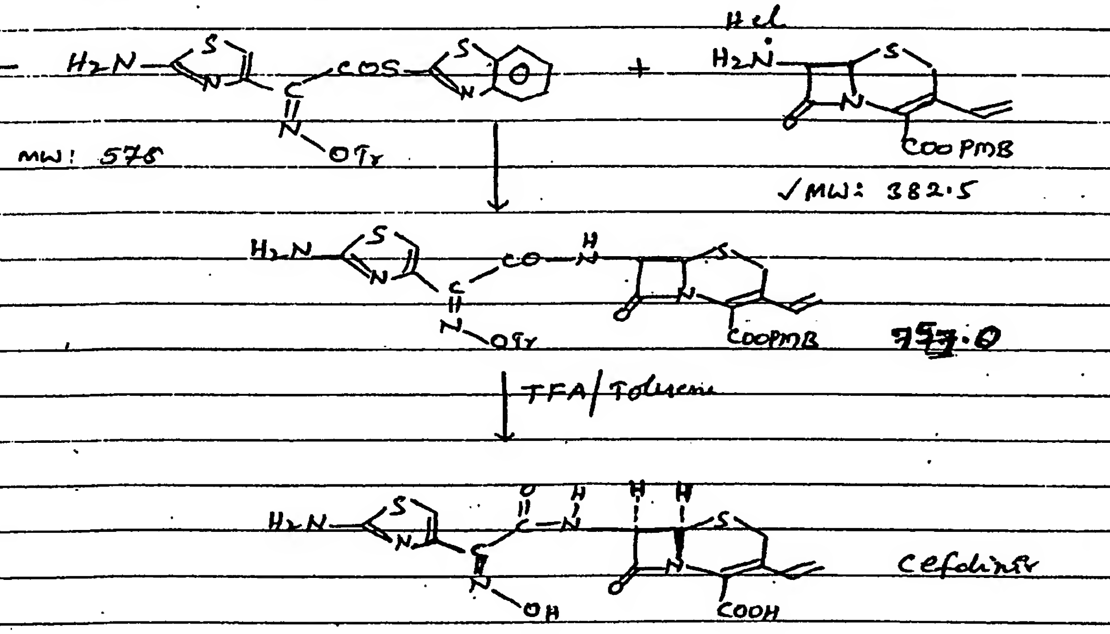
HPLC Assay (OAB): 98.45 % (M/c: 7.59 %)

IMP Reaⁿ

[redacted] Cefdinir PR(094) 98

Objective :- Preparation of Cefdinir. (Repitition of PR(094) 94)

Reaⁿ Seq :-



S.NO	Raw materials	mol wt	moles	Amount	Mol. ratio	Source
1	A.E. HCl salt	382.5 405	0.130	50 gm	1.0	
2	Thio ester	578	0.124	71.5 gm	~~1.0~~ 0.95	
3	DMAc	—	—	250 ml	5T	
4	CH_2Cl_2	—	—	1.25 lit	25T	
5	NaOH (1% w/v)	40		500 ml		
6	Toluene	—		1.0 lit		
7	Carban	—		10 gm		
8	TFA	114		300 ml.		
9	Toluene			400 ml.		
10	DM H_2O.			1.2 lit		
11	Aq NH3					
12	[illegible]					

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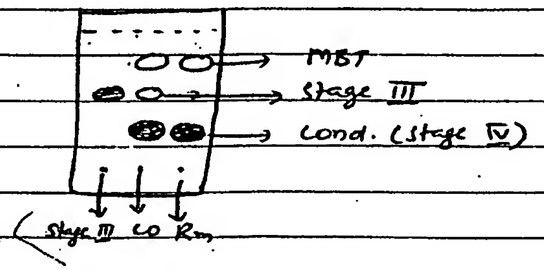
Procedures:— DMAc was added at RT.
A.E. HCl salt was added in one lot at the same temp.
The mix was stirred for 5 min, clear solution was formed ($P^H = 1.6$).
To this thioester was added in one lot at the same temp.
The mix was stirred for 10 min at 25-26°c,
P^H comes down to 1.4.
Temp was raised to 45-50°c.
Maintained for 2.0 Hrs exactly, during the maintaining P^H was maintained ~ 1.75 to 2.1 by adding TEA.
Rxn was monitored by TLC. and was showing the absence of stage III
TLC System:— EtoAc : Hexane
2.5 ml : 2.5 ml.



Then the "Rm" was cooled to RT.
"Rm" was poured into the mix of 1.0 lit H_2O + 750 ml of DCM.
The mix was stirred for 10 min at 20-25°c.
layers separated.
Aqeus layer was extracted with 500 ml of DCM.
DCM layer (combined) washed with DM H_2O (500 ml×3).
Then to the organic layer, NaOH Soln (1%, 500 ml) was added over a period of 30 min.
Stirred for 1½ Hr at 25-26°c.

The mix was Passed through the hyflow bed.
layers separated (not clear), DCM (500 ml) was added.
Organic layer washed with 200 ml DM H_2O
Then concentrated to get the Residue at 34–36°c U/ vacuum.
To the Residue, toluene was added (1.0 lit).
Again distilled the toluene (200 ml), to remove the traces of DCM
Toluene layer washed with H_2O (200 ml × 2).
Carbon (5 gm) was added to the organic (toluene) layer.
stirred for 15 mins at 30–35°c.
filtered through the hyflow bed, washed with 50 ml of toluene.
Toluene was distilled off U/Vacum till 600 ml of toluene was remains inside the flask (To remove the water).

⟹ Organic layer was Kept for over night at RT.

Organic layer was cooled to 10°c.
TFA (300 ml) was added Over a Period of 10–15 mins at 10–15
After the addn is completed, the temp was raised to 18–19°c.
Maintained for 3.15 Hrs., Toluene (400 ml) was added.
Then the reas mix was cooled to 0–5°c.
DM H_2O (1000 ml) was added at below 20°c. Over a Period of
* Temp should be 18–20°c (at the end of the H_2O addn).
After the addn immediately layer separated.
Aqous layer was Kept in Ice + H_2O mix (5–10°c).
Organic layer washed with 300 ml of DM H_2O.
layer separated.
Combined ~~Organic~~ aqous layer was cooled to 0–5°c.

pH was adjusted to aq NH_3 soln (~425 ml) at below 20°c (15-20°c).
At the end of the addn pH should be 5-5.5.
At this pH Almost clear solution formed. containing brownish undissolved particles.

Now add activated carbon (5.0 gm) at 15-20°c.
Temp brings down to 10°c.
maintained for 30 min.
filter the Carbon, through hyflow bed (15 gm).
washed the bed with 50 ml of DM H_2O.
filtrate (aqous layer) was cooled to 10-15°c.
Adjust the pH 1.0 by adding conc HCl solution.
maintain the pH 1-1.1 for 1.0 Hr at 0-5°c.
filter the solid, ~~wash~~, suck dry. till last drop.
take the wet cake (85 gm) and DM H_2O (950 ml).
warm the mix to 30-32° c for 30 min.
pH was adjusted to 2.97 by adding saturated $NaHCO_3$ solution at 30°c.
Then was cooled to 5°c.
stirred at this temp for 30 min.
filtered the solid, washed the cake with 100 ml of chilled H_2O (5°c).
Dried the solid at 30-40°c U/ high Vacu. for 10 hrs.
wet wt = 56 gm
wt of the dry product = 24 gm
% M/c = 7.1
% yield from HCl salt = 49%
% yield from GCLE =
w/w yield from HCl salt = 0.48
w/w yield from GCLE = 0.36